PATENT SPECIFICATION (11) 1 537 867

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(21) Application No. 28814/76 (22) Filed 10 July 1976
(23) Complete Specification filed 4 July 1977
(44) Complete Specification published 10 Jan. 1979
(51) INT CL² C07D 211/56
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C2C 1532 215 220 222 226 22Y 250 251 25Y 280 281 30Y 311 31Y 342 34Y 364 36Y 579 601 603 62X 634 662 697 699 KF KP

(72) Inventor GEORGE OLIVER WESTON

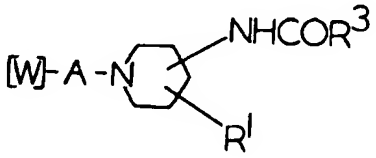
(19)

(54) PROCESS FOR PREPARING 4-ACYLAMINO-PIPERIDINE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, a British Company of Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a novel process for preparing piperidine derivatives.

In our U.K. Specification 1,345,872 we have described pharmaceutical compositions containing *inter alia* compounds of formula



I

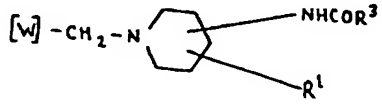
where W represents a cycloalkyl radical containing five to seven ring carbon atoms or an aryl or heteroaryl radical other than an indolyl radical, all of which radicals may be substituted or unsubstituted; A represents a lower alkylene radical, R^1 represents hydrogen, halogen or lower alkyl, and R^3 represents a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryl-lower alkyl, diaryl-lower alkyl, cycloalkyl containing 5 to 7 ring carbon atoms, lower alkoxy, or a lower alkyl radical, and acid addition and quaternary ammonium salts thereof, and the term "lower" as used therein means the radical contains from 1—6 carbon atoms.

Several methods for preparing these compounds are described including reduction of a compound of formula IIa to a compound of formula IIb and then further reduction to a compound of formula I

ERRATA

SPECIFICATION No. 1,537,867

Page 3, line 22, *for* (185 l) *read* (185 g)
Page 4, line 40, *delete* existing formula *insert*



THE PATENT OFFICE
4th June, 1979

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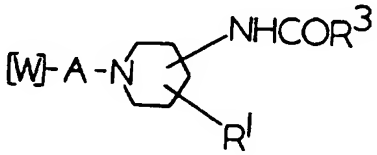

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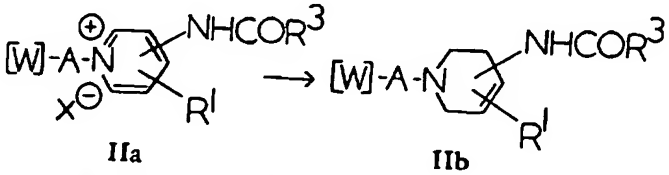
Several methods for preparing these compounds are described including reduction of a compound of formula IIa to a compound of formula IIb and then further reduction to a compound of formula I



IIa IIb

In the above formulae the symbols W, R^1, R^3, and A have the same values as given for formula I and X is an anion.

Thus as disclosed in Specification 1,345,872 a pyridinium compound of general formula II(a) may be reduced with an alkali metal borohydride to a tetrahydropyridine compound of general formula II(b). On the other hand, catalytic hydrogenation, e.g. in the presence of a Raney nickel or a platinum catalyst, reduces a pyridinium compound of formula IIa or a tetrahydropyridine compound of formula IIb to a piperidine compound of formula I. More drastic reduction of a compound of formula IIa or IIb with lithium aluminium hydride, e.g. on the tetrahydropyridine ring system, will produce compound I but also causes reduction of the double bonded oxygen group in

the COR^3 radical to give a radical $—CH_2R^3$.

We have now surprisingly found that under certain conditions it is possible to reduce a compound of formula II(a) right through to a compound of formula I using an alkali-metal borohydride e.g. sodium borohydride. This process has advantages in commercial production since it avoids the necessity for catalytic hydrogenation on a plant scale. The new method also does not cause reduction of the carbonyl group on an amide link or removal of groups susceptible to hydrogenolysis such as benzyloxycarbonyl.

Accordingly, the present invention provides a process for preparing compounds of general formula I as defined above, and acid addition and quaternary ammonium salts thereof, which process comprises treating a compound of formula II(a) or II(b) wherein [W], A, R^1 and R^3 are as defined in connection with formula I and $X^\ominus$ is an anion, with an alkali-metal borohydride in a secondary alkanol of 3 to 6 carbon atoms to cause reduction of the pyridinium ring of compound II(a) or the tetrahydropyridine ring of compound II(b) to give a compound of formula I and if desired converting the product to an acid addition or quaternary ammonium salt.

The solvent is a secondary alkanol of 3 to 6 carbon atoms especially secondary alcohols of 3 to 5 carbon atoms e.g. isopropanol, sec-butanol and pentan-2-ol. Isopropanol is preferred.

The reduction may be carried out at a temperature in the range from 60° to 165° C, preferably 80 to 120° C. Conveniently the reduction is effected in the chosen solvent at reflux temperature.

Preferably the alkali-metal borohydride is employed in a molar ratio of from 1 mol per double bond in each mol of starting material. Thus for a starting compound of formula II(a) at least 3 mols of borohydride are preferred per mol of starting material, for a starting material with formula II(b), at least one mol of borohydride per mol of starting material is preferred. If desired an excess of borohydride can be used.

However, it has been found for a starting material of formula II(a) quite good yields (e.g. of the order of 75%) can be obtained with 2 mols borohydride per mol of compound IIa. Reasonable yields are obtainable with even lesser amounts. Hence the desirable amounts are at least 0.25 mol borohydride per double bond for compound IIa or IIb, plus in the case of compound IIa an additional 1 mol for the quaternary salt which acts in a similar manner to a Lewis acid.

Examples of groups W, A, R^1, R^3 and $X^\ominus$ are the same as those given in Patent Specification No. 1,345,872.

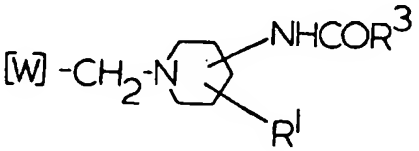
Examples of W are unsubstituted phenyl or phenyl substituted by one or more groups, which may be the same or different selected from halogen (for example fluorine, chlorine or bromine), lower alkyl (for example methyl, ethyl, propyl, or butyl), lower alkoxy (for example methoxy, ethoxy, propoxy or butoxy), nitro, amino (including alkyl or dialkyl substituted amino groups) in particular dialkylamino (for example dimethylamino or diethylamino), acylamino in particular alkanoylamino [for example acetylamino (acetamido)], hydroxyl, carboxyl, lower alkoxycarbonyl, alkylenedioxy (for example methylenedioxy), trihaloalkyl (for example trifluoromethyl), mercapto, methylthio, methylsulphonyl, phenyl and phenyl substituted by one or more of those substituents mentioned immediately above in connection with the substituted phenyl group W. Further examples of W are cycloalkyl (for example cyclohexyl), 1,2,3,4-tetrahydronaphth-6-yl, naphthyl and indenyl radicals which may be unsubstituted or substituted as described above for the substituted phenyl group W, and heterocyclic radicals such as thienyl (for example 2-thienyl), benzo [b]thienyl (for example 3-benzo[b]thienyl), furyl, pyrrolyl (for example 3-pyrrolyl), imidazolyl (for example 4-imidazolyl), pyrazolyl (for example 4-pyrazolyl), pyridyl (for example 2- and 4-pyridyl), pyrimidinyl (for example 4-pyrimidinyl), quinolyl (for example 2-quinolyl), thiazolyl (for example 2-, 4- and 5-thiazolyl), isothiazolyl, oxazolyl, isoxazolyl, benzimidazolyl (for example 2-benzimidazolyl), benzo-1, 4-dioxanyl (for example benzo-1, 4-dioxan-2-yl) and benzindolyl in particular benz[g] indolyl (for example 3-benz[g]indolyl), which heterocyclic radicals may be unsubstituted or substituted as described above for the substituted phenyl group W. Examples of A are methylene, ethylene, propylene, butylene. Examples of R^1 are hydrogen, fluorine, chlorine, bromine, methyl, ethyl, propyl and butyl. Examples of R^3 are the same as those already described for the aryl and heteroaryl radicals W and also methoxy, ethoxy, propoxy, butoxy, benzyl, phenethyl, diphenylmethyl, cyclopentyl, cyclohexyl, cycloheptyl, methyl, ethyl, propyl and butyl. Examples of acid addition salts are those formed from inorganic and organic acids in particular pharmaceutically acceptable acid

phosphate, sulphonate (such as the methane-sulphonate and p-toluene-sulphonate), acetate, maleate, fumarate, tartrate and formate.

X is preferably a halide ion such as a chloride or bromide. R^3 or W when cycloalkyl is preferably cyclohexyl.

The products of this invention are of value as pharmaceuticals as described in our U.K. Patent Specification 1,345,872, for instance as hypotensive or anti-hypertensive agents or antihistamine agents.

The process of the invention also provides a convenient way of preparing compounds of formula III



III

especially when W is aryl or heteroaryl. For instance a simple compound of formula I which may be prepared by the process of the invention is 4-benzamido-1-benzylpiperidine. Such a compound would be difficult to prepare by catalytic hydrogenation of a corresponding compound of formula IIa or IIb in view of the danger of hydrogenolysis of the 1-benzyl group to give 4-benzamido piperidine.

The starting materials of formula II(a) or II(b) may be prepared as described in U.K. specification 1,345,872.

The invention is illustrated by the following examples. Temperatures are in °C.

EXAMPLE 1.

A 5 l flanged flask, fitted with an anchor stirrer, thermometer, reflux condenser and dropping funnel is charged with isopropanol (2 l), 1-benzyl-4-benzamido pyridinium chloride (185 l) and sodium borohydride (65 g). The mixture is heated to reflux and refluxed for 3 hours with vigorous agitation. The resulting thick suspension is cooled to 30° in a water bath and water (2 l) is added, cautiously at first in view of the danger of frothing. The contents are stirred overnight and the product is then filtered off, rinsed on the filter with hot water (4 × 250 ml) and dried in a vacuum or air oven at 60—90°. The product 1-benzyl-4-benzamidopiperidine (yield 158 g, 93%) had m.p. 175—180°.

EXAMPLE 2.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-acetamidopiperidine.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-4-acetamidopyridinium iodide (1 mol) is treated with sodium borohydride (3 mols) following the procedure of Example 1 to give the title compound.

EXAMPLE 3.

1-Phenethyl-4-benzamidopiperidine.

1-[2-Phenethyl]-4-benzamidopyridinium bromide (1 mol) is treated with sodium borohydride (3 mols) following the procedure of Example 1 to give the title compound.

EXAMPLE 4.

1-[4-(p-Fluorophenyl)-butyl]-4-benzamidopiperidine.

1-[4-(p-Fluorophenyl)-butyl-4-benzamidopyridinium bromide is prepared from 4-benzamidopyridine and 4-(p-fluorophenyl) butyl bromide. The product (1 mol) is reduced with sodium borohydride (3 mols) following the procedure of Example 1.

EXAMPLE 5.

4-Benzamido-1-[2-(2-naphthyl)ethyl]piperidine.

4-Benzamido-1-[2-(2-naphthyl)ethyl]pyridinium chloride is prepared from 4-benzamidopyridine and 2-(2-naphthyl) ethyl chloride. The product (1 mol) is reduced with sodium borohydride (3 mols) according to the procedure of Example 1 to give the title compound.

EXAMPLE 6.

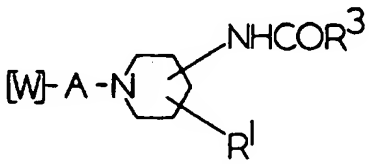
1-Phenethyl-4-benzamidopiperidine.

1-Phenethyl-4-benzamido-1,2,5,6-tetrahydropyridine (1 mol) is treated with

sodium borohydride (1 mol) according to the procedure of Example 1 to give the title compound.

WHAT WE CLAIM IS:—

1. A process for preparing compounds of general formula I



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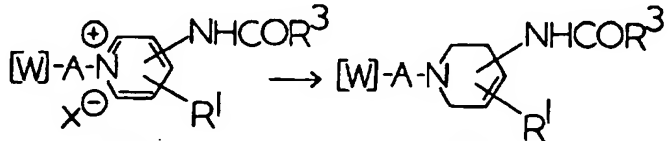
where W represents a cycloalkyl radical containing five to seven ring carbon atoms or an aryl or heteroaryl radical other than an indolyl radical, all of which radicals may be substituted or unsubstituted; A represents a lower alkylene radical, R^1 represents hydrogen, halogen or lower alkyl, and R^3 represents a substituted or unsubstituted aryl radical (including heteroaryl radicals), aryl-lower alkyl, diaryl-lower alkyl, cycloalkyl containing 5 to 7 ring carbon atoms, lower alkoxy, or a lower alkyl radical, and acid addition and quaternary ammonium salts thereof, and the term "lower" as used herein means the radical contains from 1—6 carbon atoms, which process comprises treating a compound of formula IIa or IIb



IIa IIb

wherein W, R^1, R^3, and A are as defined in connection with formula I and X is an anion, with an alkali-metal borohydride in a secondary alkanol of 3 to 6 carbon atoms to cause reduction of the pyridinium ring of compound II(a) or the tetrahydropyridine ring of compound II(b) to give a compound of formula I and if desired converting the product to an acid addition or quaternary ammonium salt.

2. A process as claimed in Claim 1, wherein W in the starting compound is a phenyl or substituted phenyl group.

3. A process as claimed in Claim 1, wherein W—A— in the starting compound is a benzyl group.

4. A process as claimed in Claim 1, wherein W in the starting compound is a naphthyl group.

5. A process as claimed in any one of Claims 1 to 4, wherein R^3 is a phenyl or substituted phenyl group.

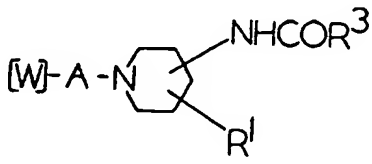
6. A process as claimed in any one of the preceding claims wherein the alkali-metal borohydride is employed in a molar ratio of from 1 mol per double bond in each mol of starting material of formula IIa or IIb.

7. A process as claimed in any one of the preceding claims wherein the solvent is a secondary alcohol of 3 to 5 carbon atoms.

8. A process as claimed in any one of Claims 1 to 6, wherein the solvent is isopropanol.

9. A process as claimed in Claim 1, substantially as hereinbefore described in any one of the specific examples.

10. A process as claimed in any one of Claims 1 to 6 wherein A in the starting compound is $—CH_2—$ and the product has formula III



wherein W, R^1 and R^3 are as previously defined.

11. A process as claimed in Claim 1, which comprises reducing a 1-benzyl-4-

benzamido pyridinium halide with an alkali metal borohydride in a secondary alkanol of 3 to 5 carbon atoms to give 1-benzyl-4-benzamido-piperidine.

12. A process as claimed in Claim 11 wherein 1-benzyl-4-benzamido pyridinium chloride is reduced with sodium borohydride in isopropanol to give 1-benzyl-4-benzamido-piperidine.

13. A compound of formula I or an acid addition or quaternary ammonium salt thereof whenever prepared by a process as claimed in any one of Claims 1 to 6, or 8 to 12.

14. A compound of formula I or an acid addition or quaternary ammonium salt thereof whenever prepared by a process as claimed in Claim 8.

G. R. PORTER,
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